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File No. 1010/16104-US4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): HOWARD L. WEINER *et al.*

Serial No.: 08/279,275

Examiner: P. Achutamurthy

Filed: July 22, 1994

Group Art Unit: 1816

For: TREATMENT OF AUTOIMMUNE DISEASES BY ORAL ADMINISTRATION
OF AUTOANTIGENS

THIRD DECLARATION OF HOWARD L. WEINER

I, HOWARD L. WEINER, do hereby declare:

1. I hold a M.D. degree, conferred by the University of Colorado in 1969.
2. I am currently Robert L. Kroc Professor of Neurology at Harvard Medical School, and have held the Robert L. Kroc Chair in Neurological Diseases since 1985. I am also appointed as Physician in Medicine (Neurology) at Brigham & Women's Hospital, Boston, MA, and have held this appointment since 1987. Since 1985, I have been Co-Director of the Center for Neurologic Diseases at the same hospital. I am also a co-inventor

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named on the patent application indicated above. A copy of my *curriculum vitae* is attached at Tab A.

3. I have extensive experience in the immunology of autoimmune diseases, including the treatment of such diseases using various immunosuppressive agents.

4. The Examiner at the U.S. Patent and Trademark Office who is in charge of this application has issued a rejection of claims on the basis of "lack of enablement." I have been informed that this rejection is based on the proposition that the treatment of the present invention, i.e., oral administration of autoantigens, is not generally useful with respect to T-cell mediated autoimmune diseases. I have also been informed that the Examiner takes that position that the experiments described in the above referenced patent application would have been understood to be substantially limited to treatment of EAE (or multiple sclerosis) and not applicable to treatment of T-cell mediated autoimmune disease by oral administration of autoantigens, as is presently claimed. The Examiner states that in view of the varying etiologies for T-cell mediated diseases, the method described in my application would not be thought applicable to those diseases in general.

5. I disagree with these conclusions. It is my opinion that an immunologist in this field would have understood, based on the teachings in the specification of my patent application, that the method of orally administering autoantigens is not limited to treatment of EAE or multiple sclerosis, but is generally applicable to T-cell mediated autoimmune disease treatment.

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6. T-cell mediated autoimmune diseases involve common pathways of immune cell activation. Because of these common pathways, it is conventional that immunosuppressive treatments are useful in treating T-cell mediated autoimmune diseases as a class, despite the fact that etiologies differ for the diseases. In other words, a single immunosuppressive type of treatment is normally believed by skilled immunologists to have general utility in treating T-cell mediated autoimmune conditions. Such immunosuppressive treatments act on cells involved with the immune responses that cause T-cell mediated autoimmune diseases, irrespective of the etiologies of the diseases.

7. There are many well-known examples of such treatments, both for human T-cell mediated autoimmune conditions and for animal models for those diseases.

8. For example, the immunosuppressive treatment cyclosporin has been used to treat T-cell mediated autoimmune diseases having differing etiologies, such as autoimmune uveitis, psoriasis, rheumatoid arthritis, and Crohn's disease (Tab B; Goodman and Gilman's; p. 1299, col. 2, ¶ 1). It has also been used in clinical trials to treat the T-cell mediated autoimmune disease type I diabetes (Tab C; Mahon et al., *Lessons Learned from Use of Cyclosporin for Insulin-Dependent Diabetes Mellitus, in Immunosuppressive and Anti-inflammatory Drugs, Annals New York Academy of Sciences*, 1993, 696:351-363). Cyclosporin has also been shown to be effective in the treatment of myasthenia gravis (Tab D; Tindall et al., *NEJM*, 316:719 (1987)).

9. Similarly, the immunosuppressive agent cyclophosphamide has been

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found to be "useful in treating a variety of autoimmune disorders", including T-cell mediated diseases such as systemic lupus erythematosus, Wegener's granulomatosis, and rheumatoid arthritis. (Tab B, Goodman and Gilman's; p. 1302, Col. 2, ¶5). Cyclophosphamide is also used to treat multiple sclerosis, and I have successfully used it for this purpose in my own medical practice. It can also be used to treat myasthenia gravis. (Tab E, Harrison's Principles of Internal Medicine, 1998, p. 2472).

10. Similarly, the immunosuppressive agent methotrexate has been used in the treatment of a variety of T-cell mediated autoimmune disorders, including multiple sclerosis, rheumatoid arthritis, psoriasis, and Wegener's granulomatosis (Tab E, Harrison's Principles of Internal Medicine, 1998, ps. 2417, 1886, 300-301, and 1916-1917, respectively).

11. In like manner, the immunosuppressive agent azathioprine "has been used to treat autoimmune diseases", such as rheumatoid arthritis and multiple sclerosis. (Tab A, Goodman and Gilman's; p. 1301; col. 2, ¶1; Tab F, Yudkin et al., Overview of Azathioprine Treatment of Multiple Sclerosis, *The Lancet*, 1991, 338:1051-1055). It has also been used to treat myasthenia gravis. (Tab E, Harrison's Principals of Internal Medicine, 1988, pg. 2472, col. 1, ¶3).

12. In addition to clinically treating the several T-cell mediated diseases described above, each of these agents, and each of the agents discussed below, has been found effective in treating several animal models of T-cell mediated diseases.

13. For example, the immunosuppressive agent rapamycin has been found

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effective in treating several animal models of T-cell mediated autoimmune diseases, including: multiple sclerosis (EAE animal model), rheumatoid arthritis (collagen induced arthritis animal model and adjuvant induced arthritis model), systemic lupus erythematosus (MRL/lpr animal model), type I diabetes (NOD mouse animal model), and autoimmune uveoretinitis (experimental autoimmune uveoretinitis animal model). (See Tab G, Sehgal,

Immunosuppressive Profile of Rapamycin, in Immunosuppressive and Anti-inflammatory Drugs, *Annals New York Academy of Sciences*, 1993, 696:1-8 at page 3.)

14. The immunosuppressive agent FK-506 has been found effective in treating several animal models of T-cell mediated autoimmune diseases, including: rheumatoid arthritis (collagen induced arthritis animal model), multiple sclerosis (EAE animal model), systemic lupus erythematosus (MRL/lpr animal model), and autoimmune uveoretinitis (experimental autoimmune uveoretinitis animal model). (See Tab H, Kino et al., Discovery of FK-506 and Update, in Immunomodulating Drugs, *Annals New York Academy of Sciences*, 1993, 685:13-21 at pages 17-18.)

15. Similarly, the immunosuppressive agent 15-Deoxyspergualin has been found effective in treating animal models of T-cell mediated autoimmune diseases that include the following: rheumatoid arthritis (adjuvant induced arthritis animal model), multiple sclerosis (EAE animal model), type I diabetes (NOD mouse animal model), and systemic lupus erythematosus (MRL/lpr animal model). (See Tab I, Schorlemmer et al., Preclinical Studies with 15-deoxyspergualin in Various Animal Models for Autoimmune Diseases, in

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Immunomodulating Drugs, *Annals New York Academy of Sciences*, 1993, 685:155-174.)

16. Results obtained subsequent to the filing of this application have confirmed that, as with the immunosuppressive therapies those described above, the present invention is generally useful to treat T-cell mediated autoimmune disease. I understand that evidence has already been submitted in this application of use of oral tolerance (the mechanism of the present invention) to treat autoimmune uveoretinitis, rheumatoid arthritis, and type I diabetes. The invention has also been found useful to treat the animal model of myasthenia gravis.

17. This represents a substantial showing, and is similar to that which exists for the immunosuppressive agents described above which have been shown to be generally useful in the treatment of T-cell mediated autoimmune diseases.

18. For these reasons, I disagree that the present invention is not shown to be generally applicable to treatment of T-cell mediated autoimmune disease, despite the differing etiologies of those diseases. As shown above, use of the same immunosuppressive treatment for T-cell mediated autoimmune diseases in general is common in this field. The available evidence indicates that the present invention is also generally applicable to such treatment.

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I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date

6/8/98

Howard L. Weiner, M.D.

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